

Public Assessment Report

Paclitaxel 6mg/ml Concentrate for Solution for Infusion

PL 04543/0487

PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 04543/0487

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted CP Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Paclitaxel 6mg/ml Concentrate for Solution for Infusion (PL 04543/0487). This is a prescription only medicine [POM] used to treat various types of cancer, including ovarian cancer, breast cancer, lung cancer and a type of cancer known as AIDS-related Kaposi's sarcoma.

This product contains the active substance paclitaxel which belongs to a group of anticancer medicines known as cytotoxics.

The clinical data presented to the MHRA, before licensing, demonstrated that Paclitaxel 6mg/ml Concentrate for Solution for Infusion is essentially similar or equivalent to the approved product, Taxol 6mg/ml Concentrate for Solution for Infusion, and as such can be used interchangeably.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using Paclitaxel 6mg/ml Concentrate for Solution for Infusion outweigh the risks, hence a Marketing Authorisation has been granted.

**PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR
INFUSION**

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a Marketing Authorisation for the medicinal product Paclitaxel 6mg/ml Concentrate for Solution for Infusion (PL 04543/0487) to CP Pharmaceuticals Limited on 5 July 2006. Paclitaxel 6mg/ml Concentrate for Solution for Infusion is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Taxol 6mg/ml Concentrate for Solution for Infusion, which was first authorised in the UK on 18 November 1993.

This product contains the active ingredient paclitaxel and is indicated for the treatment of ovarian carcinoma, breast carcinoma, advanced non-small cell lung carcinoma and AIDS-related Kaposi's sarcoma, as described in the SPC.

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

PHARMACEUTICAL ASSESSMENT

LICENCE No.: PL 04543/0487
PROPRIETARY NAME: Paclitaxel 6mg/ml Concentrate for Solution for Infusion
ACTIVE: Paclitaxel
COMPANY NAME: CP Pharmaceuticals Limited
EC ARTICLE: 10.1(a)iii
LEGAL STATUS: POM

INTRODUCTION

Legal basis

This is an abridged application for Paclitaxel 6mg/ml Concentrate for Solution for Infusion, vial sizes 30mg (5ml), 100mg (16.7ml), 150mg (25ml) and 300mg (50ml).

It may be considered that since the dose is administered on a milligramme per kg basis, all vial sizes are just different pack sizes and can be on the same marketing authorisation. All vial sizes are for multi-dose use.

The applicant claims essential similarity, under article 10.1(a)iii, first paragraph, to Taxol 6mg/ml Concentrate for Solution for Infusion (PL 11184/0026). The reference product PL 11184/0026 includes the following pack sizes: 5ml, 16.7ml, 25ml and 50ml. These packs contain the same concentration of active substance in the same pharmaceutical form and therefore acceptable under one application.

Use

The applicant has proposed indications that are consistent with those of the reference product.

QUALITY OVERALL SUMMARY (QOS)

This is satisfactory.

DRUG SUBSTANCE

Drug master files (DMFs) have been submitted for assessment of the sources of the drug substance, paclitaxel. These have been accepted as satisfactory.

General information

Description

Paclitaxel is an odourless, white to almost white powder. It is insoluble in water, slightly soluble in octanol and soluble in macrogolglycerol ricinoleate, ethanol, macrogol, chloroform, acetone and methanol.

Molecular formula: C₄₇H₅₁NO₁₄

Molecular weight: 853.9
Physical form: A white, crystalline powder.
Chirality: There are 11 chiral centres.

Drug substance specification

A satisfactory drug substance specification to be applied by the finished product manufacturer on receipt has been provided.

DRUG PRODUCT

Description and composition of the drug product

The qualitative composition of the products is as stated in the following table.

Ingredients	Function
Paclitaxel	Active substance
Macrogolglycerol ricinolate	Solubilising agent
Citric acid anhydrous	pH adjuster
Ethanol, 96%	Solvent
Nitrogen	Protective gas

Macrogolglycerol ricinolate is also known as polyoxyl castor oil and is traded as Cremophor EL. The vial sizes contain the same bulk solution and are thus proportionally identical. A similar composition has already been on the EU market for over a decade and marketed as Taxol. The qualitative formula is identical to Taxol except for the presence of citric acid. The composition is therefore acceptable.

The product is filled into colourless vials of Type I according to the Ph.Eur. with nominal capacities of 5ml, 20ml and 50ml. The vials are closed with dark grey fluropolymer-coated halobutyl rubber stoppers.

Nitrogen is used in order to create a low oxygen atmosphere during manufacture and packaging into the vial, and as a pressure aid during aseptic filtration.

No clinical trials have been carried out. This is a parenteral product containing the same active substance in the same concentration and comparable excipients as the currently marketed product Taxol. A bioequivalence study is not required according to the CPMP guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). This is accepted.

Pharmaceutical development

Drug substance

The drug substance is formulated as a non-aqueous solution with macrogolglycerol ricinolate and ethanol.

Excipients

There are no novel or unusual excipients in the formulation. The excipients have been chosen based on the reference product and accepted. The formulation is qualitatively the same as the marketed product Taxol except for the inclusion of citric acid in this formulation.

Formulation development

The composition of Paclitaxel 6mg/ml Concentrate for Solution for Infusion is based on the innovator's product Taxol 6mg/ml Concentrate for Solution for Infusion.

Manufacturing process development

The product is manufactured using normal manufacturing methods and processes for parenteral products that are susceptible to thermal degradation.

Container closure system

It is stated that the primary packaging materials comply with ISO 8362. The stability studies have proven that the quality is suitable for the intended use. This is accepted. Satisfactory stability data provides an assurance of protection from moisture and product compatibility.

Microbiological attributes

The product is a non-aqueous solution and alcohol acts as an antimicrobial. From a microbiological perspective, the shelf life of the product is supported by long-term stability studies. Data is presented to show that the product meets the acceptance criteria for parenteral products Category A. This data is also used to justify the 28 days in-use shelf life after first use (undiluted concentrate). This is accepted.

Administration

Section 6.6 of the SPC is in line with that of the reference product.

Manufacture

Manufacturer

The batch release site is Ebewe Pharma Ges.m.b.H Nfg.KG, Unterach, Austria.

Manufacturer's licences have been provided for the site of manufacture and batch release of the proposed product to assure compliance with GMP as required by current guidelines. The manufacturer is approved to manufacture a number of products for the UK market that use a similar manufacturing process to the proposed product.

Description of manufacturing process and process controls

The production process is straightforward and usual for parenteral preparations for which heat treatment is not possible.

Process validation and/or Evaluation

Full descriptions of the process validation procedures are provided, with validation reports. These are satisfactory.

Control of excipients

All of the excipients used are of Ph.Eur. quality. Specifications and Certificates of Analysis from the finished product manufacturer are provided.

Excipients of human or animal origin

The applicant states that none of the ingredients are of animal origin. The product is therefore Annex III according to MCA (*now MHRA*) letter dated 7 July 2000.

Novel excipients

There are no novel excipients.

Control of drug product

Specification

The finished product specification generally complies with ICH guidelines, Ph.Eur. requirements for sterile concentrates for injection or infusion, USP monograph for Paclitaxel Injection and the reference product.

Analytical procedures and validation

Appropriate details of test methods are provided, along with validation data. These are satisfactory.

Batch analysis

Batch analysis data are provided. All of the batches presented met the specification.

Reference standards or materials

A satisfactory Certificate of Analysis is provided for the analytical reference standard.

Container closure system

The products are packaged in Ph.Eur. Type I glass vials (nominal capacities of 5ml, 20ml and 50ml) with fluropolymer-coated chlorobutyl rubber stoppers. The glass vials and the rubber stoppers comply with the requirements of the Ph.Eur. and DIN ISO 8362. The vials are sealed with aluminium crimp cans.

Schematics of the packaging components have been provided.

Satisfactory stability data have been provided using the glass vials and rubber stoppers proposed for marketing. All results are satisfactory and within the requirements.

Quality specifications

The specifications of the glass vials, stoppers and seals have been provided. The requirements are acceptable.

Batch analysis results

Certificates of Analysis for the Type I glass vials, rubber closures and seals, showing conformance to the specifications, have been provided.

Stability

A shelf life of 2 years and special storage condition “Do not store above 25°C” are proposed. This is acceptable.

The storage conditions comply with ICH guidelines and are 25°C/60%RH and 40°C/75%RH. All results studied at both long term and accelerated conditions comply with the end-of-shelf-life specification.

The applicant has provided a commitment to continuing the long-term stability studies.

A photostability study was undertaken and the data is provided. The study is in accordance to the CPMP/ICH Guideline on Photostability Testing of New Active Substances and Medicinal Products 3AQ18a. The quality specification is as given in the finished product specification and the range of tests is considered acceptable. The results presented concluded that the drug product in the primary packaging material is photostable.

In-use shelf life

Prior to infusion Paclitaxel 6mg/ml Concentrate for Solution for Infusion must be diluted in appropriate intravenous solutions to an appropriate concentration in the range of 0.3-1.2 mg/ml. The data provided shows that the diluted product at the initial time point (of the stability study) was chemically and physically stable for 24 hours at 25°C when stored in glass bottles.

ESSENTIAL SIMILARITY

The following data are provided to support the claim for essential similarity

1. Satisfactory comparative impurity profiles are provided for the test and reference products.
2. The active substance complies with the USP.
3. The Finished Product Specification complies with ICH and Ph.Eur. general requirements and impurities are in line with the USP requirements for Paclitaxel Injection.

Essential similarity is considered proven.

NAME AND APPEARANCE

The appearance is generally in line with the reference product and accepted.
The name is suitably generic and acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS PATIENT INFORMATION LEAFLET TECHNICAL LEAFLET LABELLING

Satisfactory.

CONCLUSION

A marketing authorisation may be granted for this product.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required.

CLINICAL ASSESSMENT

LICENCE No.: PL 04543/0487
PROPRIETARY NAME: Paclitaxel 6mg/ml Concentrate for Solution for Infusion
ACTIVE: Paclitaxel
COMPANY NAME: CP Pharmaceuticals Limited
EC ARTICLE: 10.1(a)iii
LEGAL STATUS: POM

INTRODUCTION

Paclitaxel is a member of the taxane group of antineoplastic agents. It is derived from the bark and needles of the Pacific Yew Tree *Taxus brevifolia*, and is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. Paclitaxel therefore inhibits the normal dynamic reorganisation of the intracellular microtubule network essential for interphase and mitotic cellular functions.

This application is presented as an essentially similar product to Taxol 6mg/ml Concentrate for Solution for Infusion currently licensed to Bristol-Myers Squibb Pharmaceuticals Limited.

BACKGROUND

Bristol-Myers Squibb was granted a product licence (PL 11184/0026) for their Taxol 6mg/ml concentrate for solution for infusion on 18 November 1993. Thus the 10-year rule has been fulfilled.

INDICATIONS

As per Summary of Product Characteristics (SPC) Section 4.1.

DOSE AND DOSE SCHEDULE

The recommended doses and dose schedules are consistent with those for Taxol.

TOXICOLOGY

No formal data is provided under this heading and none are required for this application.

CLINICAL PHARMACOLOGY

This application does not require the inclusion of a bioequivalence study as it is an application claiming essential similarity for a parenteral drug containing the same active substance in the same concentration as the reference product.

EFFICACY

No new data are submitted and none are required for this type of application.

SAFETY

No formal safety data are presented. The adverse events that can be expected are listed in the SPC and are consistent with those for the reference product.

CLINICAL OVERVIEW

The clinical overview concludes that Paclitaxel 6mg/ml Concentrate for Solution for Infusion should be similar to the innovator product with regards to benefit and risk.

DISCUSSION

The data presented shows that Paclitaxel 6mg/ml Concentrate for Solution for Infusion is essentially similar to Taxol.

RECOMMENDATIONS

The efficacy and safety of the product are satisfactory for the grant of a marketing authorisation.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Paclitaxel 6mg/ml Concentrate for Solution for Infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

No clinical pharmacology data or clinical trials data have been submitted to directly support the claim of essential similarity of the proposed product to the proprietary product Taxol 6mg/ml Concentrate for Solution for Infusion (PL 11184/0026). This is acceptable as the formulations are similar and the same routes of administration are proposed.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of Taxol 6mg/ml Concentrate for Solution for Infusion.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk-benefit assessment is therefore considered to be favourable.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application for Paclitaxel 6mg/ml Concentrate for Solution for Infusion on 13 April 2004.
2	The MHRA's assessment of the submitted clinical data was completed on 21 October 2004.
3	Further information (clinical) was requested from the company on 22 October 2004.
4	The applicant's response to further information request (clinical) was received on 4 November 2004.
5	The MHRA's assessment of the submitted quality data was completed on 29 April 2005.
6	Further information (quality) was requested from the company on 9 May 2005.
7	The applicant's response to further information request (quality) was sent in a letter dated 12 December 2005.
8	Further information (clinical) was requested from the company on 27 February 2006 and 4 April 2006.
9	Further information (quality) was requested from the company on 3 April 2006.
10	The applicant's response to further information request (clinical) was sent in a letter dated 6 April 2006.
11	The applicant's response to further information request (quality) was sent in a letter dated 6 April 2006.
12	Further information (quality) was requested from the company on 9 May 2006.
13	The applicant's response to further information request (quality) was sent on 12 May 2006.
14	Additional information (quality) requested from the company on 23 June 2006.
15	The applicant responded to additional information request (quality) on 26 June 2006.
16	The application was determined on 5 July 2006.

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INFUSION**

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paclitaxel 6mg/ml Concentrate for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 6mg of the active ingredient, paclitaxel

1 vial of 5ml contains 30mg of paclitaxel

1 vial of 16.7ml contains 100mg of paclitaxel

1 vial of 25ml contains 150mg of paclitaxel

1 vial of 50ml contains 300mg of paclitaxel

1ml contains 525mg of the excipient, macrogol glycerol ricinolate

1 vial of 5ml contains 2.625g of macrogol glycerol ricinolate

1 vial of 16.7ml contains 8.768g of macrogol glycerol ricinolate

1 vial of 25ml contains 13.125g of macrogol glycerol ricinolate

1 vial of 50ml contains 26.250g of macrogol glycerol ricinolate

For full list of excipients, see 6.1

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

A clear, colourless to pale yellow solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ovarian carcinoma: in the first-line chemotherapy of ovarian cancer, paclitaxel infusion is indicated for the treatment of patients with advanced carcinoma of the ovary or with residual disease (> 1 cm) after initial laparotomy, in combination with cisplatin.

In the second-line chemotherapy of ovarian cancer, paclitaxel infusion is indicated for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum containing therapy.

Breast carcinoma: In the adjuvant setting, paclitaxel infusion is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and

cyclophosphamide (AC) therapy. Adjuvant treatment with paclitaxel infusion should be regarded as an alternative to extended AC therapy.

Paclitaxel infusion is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express HER-2 at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable (see 4.4 and 5.1).

As a single agent, paclitaxel infusion is indicated for the treatment of metastatic carcinoma of the breast in patients who have failed, or are not candidates for standard, anthracycline containing therapy.

Advanced non-small cell lung carcinoma: paclitaxel infusion, in combination with cisplatin, is indicated for the treatment of non-small cell lung carcinoma (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy.

AIDS-related Kaposi's sarcoma: paclitaxel infusion is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma (KS) who have failed prior liposomal anthracycline therapy.

Limited efficacy data supports this indication, a summary of the relevant studies is shown in section 5.1.

4.2. Posology and method of administration

All patients must be premedicated with corticosteroids, antihistamines, and H₂ antagonists prior to paclitaxel infusion, e.g.

Drug	Dose	Administration prior to paclitaxel infusion
dexamethasone	20 mg oral* or IV	For oral administration: approximately 12 and 6 hours or for IV administration: 30 to 60 min
diphenhydramine**	50 mg IV	30 to 60 min
cimetidine or ranitidine	300 mg IV 50 mg IV	30 to 60 min

* 8-20 mg for KS patients

** or an equivalent antihistamine e.g. chlorpheniramine

Paclitaxel infusion should be administered through an in-line filter with a microporous membrane $\leq 0.22 \mu\text{m}$ (see 6.6).

First-line chemotherapy of ovarian carcinoma: although other dosage regimens are under investigation, a combination regimen of paclitaxel infusion and cisplatin is recommended. According to duration of infusion, two doses of paclitaxel infusion are recommended: paclitaxel infusion 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin at a dose of 75 mg/m^2 every three weeks or paclitaxel infusion 135 mg/m^2 , in a 24-hour infusion, followed by cisplatin 75 mg/m^2 , with a three week interval between courses (see 5.1).

Second-line chemotherapy of ovarian carcinoma: the recommended dose of paclitaxel infusion is 175 mg/m^2 administered over a period of three hours, with a three week interval between courses.

Adjuvant chemotherapy in breast carcinoma: the recommended dose of paclitaxel infusion is 175 mg/m^2 administered over a period of three hours every three weeks for four courses, following AC therapy.

First-line chemotherapy of breast carcinoma: when used in combination with doxorubicin (50 mg/m^2), paclitaxel infusion should be administered 24 hours after doxorubicin. The recommended dose of paclitaxel infusion is 220 mg/m^2 administered intravenously over a period of three hours, with a three-week interval between courses (see 4.5 and 5.1).

When used in combination with trastuzumab, the recommended dose of paclitaxel infusion is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses (see 5.1). Paclitaxel infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated (for detailed trastuzumab posology see the Summary of Product Characteristics of trastuzumab).

Second-line chemotherapy of breast carcinoma: the recommended dose of paclitaxel infusion is 175 mg/m^2 administered over a period of three hours, with a three-week interval between courses.

Treatment of advanced NSCLC: the recommended dose of paclitaxel infusion is 175 mg/m^2 administered over a period of three hours, followed by cisplatin 80 mg/m^2 , with a three week interval between courses.

Treatment of AIDS-related KS: the recommended dose of paclitaxel infusion is 100 mg/m^2 administered as a three-hour intravenous infusion every two weeks.

Subsequent doses of paclitaxel infusion should be administered according to individual patient tolerance.

Paclitaxel infusion should not be readministered until the neutrophil count is $\geq 1,500/\text{mm}^3$ ($\geq 1,000/\text{mm}^3$ for KS patients) and the platelet count is $\geq 100,000/\text{mm}^3$ ($\geq 75,000/\text{mm}^3$ for KS patients). Patients who experience severe neutropenia (neutrophil count $< 500/\text{mm}^3$ for ≥ 7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for KS patients) (see 4.4).

Patients with hepatic impairment: Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see 4.4 and 5.2). Patients with severe hepatic impairment should not be treated with paclitaxel.

4.3. Contraindications

Paclitaxel is contra-indicated in patients with severe hypersensitivity to paclitaxel or to any ingredient, especially macrogol glycerol ricinolate (see 4.4).

Paclitaxel is contraindicated during pregnancy and lactation (see 4.6) and should not be used in patients with baseline neutrophils $< 1,500/\text{mm}^3$ ($< 1,000/\text{mm}^3$ for KS patients).

In KS, paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections.

4.4. Special warnings and precautions for use

Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.

Patients must be pretreated with corticosteroids, antihistamines and H_2 antagonists (see 4.2).

Paclitaxel should be given *before* cisplatin when used in combination (see 4.5).

Significant hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in $< 1\%$ of patients receiving paclitaxel after adequate premedication. These reactions are probably histamine-mediated. In the case of severe hypersensitivity reactions, paclitaxel should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to $\geq 1,500/\text{mm}^3$ ($\geq 1,000/\text{mm}^3$ for KS patients) and platelets recover to $\geq 100,000/\text{mm}^3$ ($\geq 75,000/\text{mm}^3$ for KS patients). In the KS clinical study, the majority of patients were receiving granulocyte colony stimulating factor (G-CSF).

Severe cardiac conduction abnormalities have been reported rarely with single agent paclitaxel. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel. Hypotension, hypertension, and bradycardia have been observed during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of

paclitaxel infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with NSCLC than in those with breast or ovarian carcinoma. A single case of heart failure related to paclitaxel was seen in the AIDS-KS clinical study.

When paclitaxel is used in combination with doxorubicin or trastuzumab for initial treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function. When patients are candidates for treatment with paclitaxel in these combinations, they should undergo baseline cardiac assessment including history, physical examination, ECG, echocardiogram, and/or MUGA scan. Cardiac function should be further monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction and treating physicians should carefully assess the cumulative dose (mg/m²) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating physicians should carefully assess the clinical benefits of further therapy against the potential for producing cardiac damage, including potentially irreversible damage. If further treatment is administered, monitoring of cardiac function should be more frequent (e.g. every 1-2 cycles). For more details see Summary of Product Characteristics of trastuzumab or doxorubicin.

Although the occurrence of *peripheral neuropathy* is frequent, the development of severe symptoms is rare. In severe cases, a dose reduction of 20% (25% for KS patients) for all subsequent courses of paclitaxel is recommended. In NSCLC patients and in ovarian cancer patients treated in the first-line setting, the administration of paclitaxel as a three hour infusion in combination with cisplatin, resulted in a greater incidence of severe neurotoxicity than both single agent paclitaxel and cyclophosphamide followed by cisplatin.

Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a three-hour infusion to patients with mildly abnormal liver function. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment. Patients should be monitored closely for the development of profound myelosuppression (see 4.2). Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see 5.2).

No data are available for patients with severe baseline cholestasis. Patients with severe hepatic impairment should not be treated with paclitaxel.

Since paclitaxel 6mg/ml infusion contains ethanol (396 mg/ml), consideration should be given to possible CNS and other effects.

Special care should be taken to avoid intra-arterial application of paclitaxel, since in animal studies testing for local tolerance severe tissue reactions were observed after intra-arterial application.

Pseudomembranous colitis has been rarely reported including cases in patients who have not been concomitantly treated with antibiotics. This reaction should be considered in the differential diagnosis of cases of severe or persistent diarrhoea occurring during or shortly after treatment with paclitaxel.

Paclitaxel in combination with radiation of the lung, irrespective of their chronological order, may contribute to the development of *interstitial pneumonitis*.

In KS patients, severe mucositis is rare. If severe reactions occur, the paclitaxel dose should be reduced by 25%.

This product contains macrogol glycerol ricinolate which may cause severe allergic reactions.

4.5. Interactions with other medicinal products and other forms of interaction

Paclitaxel clearance is not affected by cimetidine premedication.

The recommended regimen of paclitaxel administration for the first-line chemotherapy of ovarian carcinoma is for paclitaxel to be given before cisplatin. When paclitaxel is given before cisplatin, the safety profile of paclitaxel is consistent with that reported for single-agent use. When paclitaxel was given after cisplatin, patients showed a more profound myelosuppression and an approximately 20% decrease in paclitaxel clearance. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynaecological cancers.

Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, paclitaxel for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin (see 5.2).

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4 (see 5.2). Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel, to 6 α -hydroxypaclitaxel, is the major metabolic pathway in humans. Concurrent administration of ketoconazole, a known potent inhibitor of CYP3A4, does not inhibit the elimination of paclitaxel in patients; thus, both medicinal products may be administered together without dosage adjustment. Further data on the potential of drug interactions between paclitaxel and other CYP3A4 substrates/inhibitors are limited. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or 3A4.

Studies in KS patients, who were taking multiple concomitant medications, suggest that the systemic clearance of paclitaxel was significantly lower in the presence of nelfinavir and ritonavir, but not with indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

4.6. Pregnancy and lactation

Paclitaxel has been shown to be embryotoxic and foetotoxic in rabbits, and to decrease fertility in rats.

There is no information on the use of paclitaxel in pregnant women. As with other cytotoxic drugs, paclitaxel may cause foetal harm, and is therefore contraindicated during pregnancy. Women should be advised to avoid becoming pregnant during therapy with paclitaxel, and to inform the treating physician immediately should this occur.

It is not known whether paclitaxel is excreted in human milk. Paclitaxel is contraindicated during lactation. Breastfeeding should be discontinued for the duration of paclitaxel therapy.

4.7. Effects on ability to drive and use machines

Paclitaxel has not been demonstrated to interfere with this ability. However, it should be noted that the formulation contains alcohol (see 4.4 and 6.1).

4.8. Undesirable effects

The frequency and severity of undesirable effects, unless otherwise mentioned, are generally similar between patients receiving paclitaxel for the treatment of ovarian carcinoma, breast carcinoma, or NSCLC. None of the observed toxicities were clearly influenced by age.

The most frequent significant undesirable effect was **bone marrow suppression**. Severe neutropenia (< 500 cells/mm³) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for 7 days. Thrombocytopenia was reported in 11% of patients. Three percent of patients had a platelet count nadir $< 50,000$ /mm³ at least once while on study. Anaemia was observed in 64% of patients, but was severe (Hb < 5 mmol/l) in only 6% of patients. Incidence and severity of anaemia is related to baseline haemoglobin status.

Neurotoxicity, mainly **peripheral neuropathy**, appeared to be more frequent and severe with a 175 mg/m² 3-hour infusion (85% neurotoxicity, 15% severe) than with a 135 mg/m² 24-hour infusion (25% peripheral neuropathy, 3% severe) when paclitaxel was combined with cisplatin. In NSCLC patients and in ovarian cancer patients treated with paclitaxel over three hours followed by cisplatin, there is an apparent increase in the incidence of severe neurotoxicity. Peripheral neuropathy can occur following the first course and can worsen with increasing exposure to paclitaxel. Peripheral neuropathy was the cause of paclitaxel discontinuation in a few cases. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

Arthralgia or myalgia affected 60% of patients and was severe in 13% of patients.

A significant hypersensitivity reaction with possible fatal outcome (defined as hypotension requiring therapy, angioedema, respiratory distress requiring

bronchodilator therapy, or generalised urticaria) occurred in two (< 1%) of patients. Thirty-four percent of patients (17% of all courses) experienced minor hypersensitivity reactions. These minor reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy.

Injection site reactions during intravenous administration may lead to localised oedema, pain, erythema, and induration; on occasion, extravasation can result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. Skin discoloration may also occur. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e. “recall”, has been reported rarely. A specific treatment for extravasation reactions is unknown at this time.

The table below lists undesirable effects regardless of severity associated with the administration of single agent paclitaxel administered as a three hour infusion in the metastatic setting.

The frequency of undesirable effects listed below is defined using the following convention:

very common ($\geq 1/10$); common ($\geq 1/100, < 1/10$); uncommon ($\geq 1/1,000, < 1/100$); rare ($\geq 1/10,000, < 1/1,000$); very rare ($< 1/10,000$).

Infections and infestations:	<i>Very common</i> : infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome <i>Uncommon</i> : septic shock <i>Rare</i> : pneumonia, peritonitis, sepsis
Blood and the lymphatic system disorders:	<i>Very common</i> : myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding <i>Rare</i> : febrile neutropenia <i>Very rare</i> : acute myeloid leukaemia, myelodysplastic syndrome
Immune system disorders:	<i>Very common</i> : minor hypersensitivity reactions (mainly flushing and rash) <i>Uncommon</i> : significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremities, diaphoresis and hypertension) <i>Rare</i> : anaphylactic reactions <i>Very rare</i> : anaphylactic shock
Metabolism and nutrition disorders:	<i>Very rare</i> : anorexia
Psychiatric disorders:	<i>Very rare</i> : confusional state
Nervous system disorders:	<i>Very common</i> : neurotoxicity (mainly: peripheral neuropathy) <i>Rare</i> : motor neuropathy (with resultant minor distal weakness) <i>Very rare</i> : autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia

Eye disorders:	<i>Very rare:</i> optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended
Ear and labyrinth disorders:	<i>Very rare :</i> ototoxicity, hearing loss, tinnitus, vertigo
Cardiac disorders:	<i>Common:</i> bradycardia <i>Uncommon :</i> cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction <i>Very rare :</i> atrial fibrillation, supraventricular tachycardia
Vascular disorders:	<i>Very common :</i> hypotension <i>Uncommon:</i> hypertension, thrombosis, thrombophlebitis <i>Very rare:</i> shock
Respiratory, thoracic and mediastinal disorders:	<i>Rare:</i> dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure <i>Very rare:</i> cough
Gastrointestinal disorders:	<i>Very common :</i> nausea, vomiting, diarrhoea, mucosal inflammation <i>Rare*:</i> bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis <i>Very rare :</i> mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, neutropenic colitis
Hepato-biliary disorders:	<i>Very rare:</i> hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)
Skin and subcutaneous tissue disorders:	<i>Very common :</i> alopecia <i>Common:</i> transient and mild nail and skin changes <i>Rare:</i> pruritus, rash, erythema <i>Very rare :</i> Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet)
Musculoskeletal, connective tissue and bone disorders :	<i>Very common:</i> arthralgia, myalgia
General disorders and administration site conditions:	<i>Common :</i> injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis) <i>Rare:</i> asthenia, pyrexia, dehydration, oedema, malaise
Investigations:	<i>Common :</i> severe elevation in AST (SGOT), severe elevation in alkaline phosphatase <i>Uncommon:</i> severe elevation in bilirubin <i>Rare:</i> increase in blood creatinine

Breast cancer patients who received paclitaxel in the adjuvant setting following AC experienced more neurosensory toxicity, hypersensitivity reactions, arthralgia/myalgia, anaemia, infection, fever, nausea/vomiting and diarrhoea than patients who received AC alone. However, the frequency of these events was consistent with the use of single agent paclitaxel, as reported above.

Combination treatment

When administered as a three hour infusion for the first-line chemotherapy of ovarian cancer, neurotoxicity, arthralgia/myalgia, and hypersensitivity were reported as more frequent and severe by patients treated with paclitaxel followed by cisplatin than patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with paclitaxel as a three hour infusion followed by cisplatin compared with cyclophosphamide followed by cisplatin.

For the first line chemotherapy of metastatic breast cancer, neutropenia, anaemia, peripheral neuropathy, arthralgia/myalgia, asthenia, fever, and diarrhoea were reported more frequently and with greater severity when paclitaxel (220 mg/m²) was administered as a three-hour infusion 24 hours following doxorubicin (50 mg/m²) when compared to standard FAC therapy (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²). Nausea and vomiting appeared to be less frequent and severe with the paclitaxel (220 mg/m²) / doxorubicin (50 mg/m²) regimen as compared to the standard FAC regimen. The use of corticosteroids may have contributed to the lower frequency and severity of nausea and vomiting in the paclitaxel/doxorubicin arm.

When paclitaxel was administered as a three-hour infusion in combination with trastuzumab for the first line treatment of patients with metastatic breast cancer, the following events (regardless of relationship to paclitaxel or trastuzumab) were reported more frequently than with single agent paclitaxel: heart failure (8% vs 1%), infection (46% vs 27%), chills (42% vs 4%), fever (47% vs 23%), cough (42% vs 22%), rash (39% vs 18%), arthralgia (37% vs 21%), tachycardia (12% vs 4%), diarrhoea (45% vs 30%), hypertonia (11% vs 3%), epistaxis (18% vs 4%), acne (11% vs 3%), herpes simplex (12% vs 3%), accidental injury (13% vs 3%), insomnia (25% vs 13%), rhinitis (22% vs 5%), sinusitis (21% vs 7%), and injection site reaction (7% vs 1%). Some of these frequency differences may be due to the increased number and duration of treatments with paclitaxel /trastuzumab combination vs single agent paclitaxel. Severe events were reported at similar rates for paclitaxel /trastuzumab and single agent paclitaxel.

When doxorubicin was administered in combination with paclitaxel in metastatic breast cancer, **cardiac contraction abnormalities** (\geq 20% reduction of left ventricular ejection fraction) were observed in 15% of patients vs. 10% with standard FAC regimen. **Congestive heart failure** was observed in < 1% in both paclitaxel /doxorubicin and standard FAC arms. Administration of trastuzumab in combination with paclitaxel in patients previously treated with anthracyclines resulted in an increased frequency and severity of **cardiac dysfunction** in comparison with patients treated with paclitaxel single agent (NYHA Class I/II 10% vs. 0%; NYHA Class III/IV 2% vs. 1%) and rarely has been associated with death (see trastuzumab Summary of Product Characteristics). In all but these rare cases, patients responded to appropriate medical treatment.

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

AIDS-related Kaposi's sarcoma

Except for haematologic and hepatic undesirable effects (see below), the frequency and severity of undesirable effects are generally similar between KS patients and

patients treated with paclitaxel monotherapy for other solid tumours, based on a clinical study including 107 patients.

Blood and the lymphatic system disorders: bone marrow suppression was the major dose-limiting toxicity. Neutropenia is the most important haematological toxicity. During the first course of treatment, severe neutropenia (< 500 cells/mm³) occurred in 20% of patients. During the entire treatment period, severe neutropenia was observed in 39% of patients. Neutropenia was present for > 7 days in 41% and for 30-35 days in 8% of patients. It resolved within 35 days in all patients who were followed. The incidence of Grade 4 neutropenia lasting ≥ 7 days was 22%.

Neutropenic fever related to paclitaxel was reported in 14% of patients and in 1.3% of treatment cycles. There were three septic episodes (2.8%) during paclitaxel administration related to the medicinal product that proved fatal.

Thrombocytopenia was observed in 50% of patients, and was severe ($< 50,000$ cells/mm³) in 9%. Only 14% experienced a drop in their platelet count $< 75,000$ cells/mm³, at least once while on treatment. Bleeding episodes related to paclitaxel were reported in $< 3\%$ of patients, but the haemorrhagic episodes were localised.

Anaemia (Hb < 11 g/dL) was observed in 61% of patients and was severe (Hb < 8 g/dL) in 10%. Red cell transfusions were required in 21% of patients.

Hepato-biliary disorders : Among patients ($> 50\%$ on protease inhibitors) with normal baseline liver function, 28%, 43% and 44% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. For each of these parameters, the increases were severe in 1% of cases.

4.9. Overdose

There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group/ATC code: cystostatic agent, L01C D01.

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

In the first-line chemotherapy of ovarian carcinoma, the safety and efficacy of paclitaxel were evaluated in two major, randomised, controlled (vs. cyclophosphamide 750 mg/m² / cisplatin 75 mg/m²) trials. In the Intergroup trial (BMS CA139-209), over 650 patients with stage II_{b-c}, III or IV primary ovarian cancer received a maximum of 9 treatment courses of paclitaxel (175 mg/m² over three hr) followed by cisplatin (75 mg/m²) or control. The second major trial (GOG-111/BMS CA139-022) evaluated a maximum of six courses of either paclitaxel (135 mg/m² over 24 hrs) followed by cisplatin (75 mg/m²) or control in over 400 patients with stage III/IV primary ovarian cancer, with a > 1 cm residual disease after staging laparotomy, or with distant metastases. While the two different paclitaxel posologies were not compared with each other directly, in both trials patients treated with paclitaxel in combination with cisplatin had a significantly higher response rate, longer time to progression, and longer survival time when compared with standard therapy. Increased neurotoxicity, arthralgia/myalgia but reduced myelosuppression were observed in advanced ovarian cancer patients administered three-hour infusion paclitaxel/cisplatin as compared to patients who received cyclophosphamide/cisplatin.

In the adjuvant treatment of breast carcinoma, 3121 patients with node positive breast carcinoma were treated with adjuvant paclitaxel therapy or no chemotherapy following four courses of doxorubicin and cyclophosphamide (CALGB 9344, BMS CA 139-223). Median follow-up was 69 months. Overall, paclitaxel patients had a significant reduction of 18% in the risk of disease recurrence relative to patients receiving AC alone (p = 0.0014), and a significant reduction of 19% in the risk of death (p = 0.0044) relative to patients receiving AC alone. Retrospective analyses show benefit in all patient subsets. In patients with hormone receptor negative/unknown tumours, reduction in risk of disease recurrence was 28% (95%CI: 0.59-0.86). In the patient subgroup with hormone receptor positive tumours, the risk reduction of disease recurrence was 9% (95%CI: 0.78-1.07). However, the design of the study did not investigate the effect of extended AC therapy beyond four cycles. It cannot be excluded on the basis of this study alone that the observed effects could be partly due to the difference in duration of chemotherapy between the two arms (AC 4 cycles; AC + paclitaxel eight cycles). Therefore, adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy.

In a second large clinical study in adjuvant node positive breast cancer with a similar design, 3060 patients were randomized to receive or not four courses of paclitaxel at a higher dose of 225 mg/m² following four courses of AC (NSABP B-28, BMS CA139-270). At a median follow-up of 64 months, Paclitaxel patients had a significant reduction of 17% in the risk of disease recurrence relative to patients who received AC alone (p = 0.006); paclitaxel treatment was associated with a reduction in the risk of death of 7% (95%CI: 0.78-1.12). All subset analyses favored the paclitaxel arm. In this study patients with hormone receptor positive tumour had a reduction in the risk of disease recurrence of 23% (95%CI: 0.6-0.92); in the patient subgroup with hormone receptor negative tumour the risk reduction of disease recurrence was 10% (95%CI: 0.7-1.11).

In the first-line treatment of metastatic breast cancer, the efficacy and safety of paclitaxel were evaluated in two pivotal, phase III, randomised, controlled open-label trials.

In the first study (BMS CA139-278), the combination of bolus doxorubicin (50 mg/m²) followed after 24 hours by paclitaxel (220 mg/m² by 3-hour infusion) (AT),

was compared versus standard FAC regimen (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²), both administered every three weeks for eight courses. In this randomised study, 267 patients with metastatic breast cancer, who had either received no prior chemotherapy or only non-anthracycline chemotherapy in the adjuvant setting, were enrolled. Results showed a significant difference in time to progression for patients receiving AT compared to those receiving FAC (8.2 vs. 6.2 months; p= 0.029). The median survival was in favour of Paclitaxel/doxorubicin vs. FAC (23.0 vs. 18.3 months; p= 0.004). In the AT and FAC treatment arm 44% and 48% respectively received follow-up chemotherapy which included taxanes in 7% and 50% respectively. The overall response rate was also significantly higher in the AT arm compared to the FAC arm (68% vs. 55%). Complete responses were seen in 19% of the Paclitaxel/doxorubicin arm patients vs. 8% of the FAC arm patients. All efficacy results have been subsequently confirmed by a blinded independent review.

In the second pivotal study, the efficacy and safety of the paclitaxel and trastuzumab combination was evaluated in a planned subgroup analysis (metastatic breast cancer patients who formerly received adjuvant anthracyclines) of the study HO648g. The efficacy of trastuzumab in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been proven. The combination of trastuzumab (4 mg/kg loading dose then 2 mg/kg weekly) and paclitaxel (175 mg/m²) 3-hour infusion, every three weeks was compared to single-agent paclitaxel (175 mg/m²) three-hour infusion, every three weeks in 188 patients with metastatic breast cancer overexpressing HER2 (2+ or 3+ as measured by immunohistochemistry), who had previously been treated with anthracyclines. paclitaxel was administered every three weeks for at least six courses while trastuzumab was given weekly until disease progression. The study showed a significant benefit for the paclitaxel /trastuzumab combination in terms of time to progression (6.9 vs. 3.0 months), response rate (41% vs. 17%), and duration of response (10.5 vs. 4.5 months) when compared to paclitaxel alone. The most significant toxicity observed with the paclitaxel /trastuzumab combination was cardiac dysfunction (see 4.8).

In the treatment of advanced NSCLC, paclitaxel 175 mg/m² followed by cisplatin 80 mg/m² has been evaluated in two phase III trials (367 patients on paclitaxel containing regimens). Both were randomised trials, one compared to treatment with cisplatin 100 mg/m², the other used teniposide 100 mg/m² followed by cisplatin 80 mg/m² as comparator (367 patients on comparator). Results in each trial were similar. For the primary outcome of mortality, there was no significant difference between the paclitaxel containing regimen and the comparator (median survival times 8.1 and 9.5 months on paclitaxel containing regimens, 8.6 and 9.9 months on comparators). Similarly, for progression-free survival there was no significant difference between treatments. There was a significant benefit in terms of clinical response rate. Quality of life results are suggestive of a benefit on paclitaxel containing regimens in terms of appetite loss and provide clear evidence of the inferiority of paclitaxel containing regimens in terms of peripheral neuropathy (p < 0.008).

In the treatment of AIDS-related KS, the efficacy and safety of paclitaxel were investigated in a non-comparative study in patients with advanced KS, previously treated with systemic chemotherapy. The primary end-point was best tumour response. Of the 107 patients, 63 were considered resistant to liposomal anthracyclines. This subgroup is considered to constitute the core efficacy population. The overall success rate (complete/partial response) after 15 cycles of treatment was 57% (CI 44 - 70%) in liposomal anthracycline-resistant patients. Over 50% of the responses were apparent

after the first three cycles. In liposomal anthracycline-resistant patients, the response rates were comparable for patients who had never received a protease inhibitor (55.6%) and those who received one at least two months prior to treatment with paclitaxel (60.9%). The median time to progression in the core population was 468 days (95% CI 257-NE). Median survival could not be computed, but the lower 95% bound was 617 days in core patients.

5.2. Pharmacokinetic properties

Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations.

The pharmacokinetics of paclitaxel were determined following three and 24 hour infusions at doses of 135 and 175 mg/m². Mean terminal half-life estimates ranged from 3.0 to 52.7 hours, and mean, non-compartmentally derived, values for total body clearance ranged from 11.6 to 24.0 l/hr/m²; total body clearance appeared to decrease with higher plasma concentrations of paclitaxel. Mean steady-state volume of distribution ranged from 198 to 688 l/m², indicating extensive extravascular distribution and/or tissue binding. With the 3-hour infusion, increasing doses result in non-linear pharmacokinetics. For the 30% increase in dose from 135 mg/m² to 175 mg/m², the C_{max} and AUC_{0-∞} values increased 75% and 81%, respectively.

Following an intravenous dose of 100 mg/m² given as a three-hour infusion to 19 KS patients, the mean C_{max} was 1,530 ng/ml (range 761 - 2,860 ng/ml) and the mean AUC 5,619 ng.hr/ml (range 2,609 - 9,428 ng.hr/ml). Clearance was 20.6 l/h/m² (range 11-38) and the volume of distribution was 291 l/m² (range 121-638). The terminal elimination half-life averaged 23.7 hours (range 12 - 33).

Inpatient variability in systemic paclitaxel exposure was minimal. There was no evidence for accumulation of paclitaxel with multiple treatment courses.

In vitro studies of binding to human serum proteins indicate that 89-98% of drug is bound. The presence of cimetidine, ranitidine, dexamethasone or diphenhydramine did not affect protein binding of paclitaxel.

The disposition of paclitaxel has not been fully elucidated in humans. Mean values for cumulative urinary recovery of unchanged drug have ranged from 1.3 to 12.6% of the dose, indicating extensive non-renal clearance. Hepatic metabolism and biliary clearance may be the principal mechanism for disposition of paclitaxel. Paclitaxel appears to be metabolised primarily by cytochrome P450 enzymes. Following administration of a radiolabelled paclitaxel, an average of 26, 2 and 6% of the radioactivity was excreted in the faeces as 6 α -hydroxypaclitaxel, 3'-p-hydroxypaclitaxel, and 6 α -3'-p-dihydroxy-paclitaxel, respectively. The formation of these hydroxylated metabolites is catalysed by CYP2C8, -3A4, and both -2C8 and -3A4 respectively. The effect of renal or hepatic dysfunction on the disposition of paclitaxel following a 3-hour infusion has not been investigated formally.

Pharmacokinetic parameters obtained from one patient undergoing haemodialysis who received a three-hour infusion of paclitaxel 135 mg/m² were within the range of those defined in non-dialysis patients.

In clinical trials where paclitaxel and doxorubicin were administered concomitantly, the distribution and elimination of doxorubicin and its metabolites were prolonged. Total plasma exposure to doxorubicin was 30% higher when paclitaxel immediately followed doxorubicin than when there was a 24-hour interval between drugs.

For use of paclitaxel in combination with other therapies, please consult the Summary of Product Characteristics of cisplatin, doxorubicin or trastuzumab for information on the use of these medicinal products.

5.3. Preclinical safety data

The carcinogenic potential of paclitaxel has not been studied. However, paclitaxel is a potential carcinogenic and genotoxic agent, based upon its pharmacodynamic mechanism of action. Paclitaxel has been shown to be mutagenic in both *in vitro* and *in vivo* mammalian test systems.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric acid, anhydrous
Macrogol glycerol ricinolate
Ethanol, 96%
Nitrogen

6.2. Incompatibilities

Macrogol glycerol ricinolate can result in DEHP [di-(2-ethylhexyl)phthalate] leaching from plasticised polyvinyl chloride (PVC) containers, at levels which increase with time and concentration. Consequently, the preparation, storage and administration of diluted paclitaxel concentrate should be carried out using non-PVC-containing equipment.

6.3. Shelf life

Under recommended storage conditions, the unopened product is stable for up to 24 months

For diluted solution, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Diluted solution should be for single use only.

6.4. Special precautions for storage

Do not store above 25°C.

After dilution:

Chemical and physical in use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 25°C. Other in use storage times and conditions are the responsibility of the user.

The diluted solution should not be refrigerated or frozen

6.5. Nature and contents of container

Colourless Type I glass vial with fluropolymer-coated chlorobutyl rubber stoppers and aluminium overseal.

Packs of 1 vial containing 5ml, 16.7ml, 25ml and 50ml of Paclitaxel 6mg/ml Concentrate for Solution for Infusion.

6.6 Special precautions for disposal

Handling: as with all antineoplastic agents, caution should be exercised when handling Paclitaxel 6mg/ml Concentrate for Solution for Infusion. Dilution should be carried out under aseptic conditions by trained personnel in a designated area. Adequate protective gloves should be worn. Precautions should be taken to avoid contact with the skin and mucous membranes. In the event of contact with the skin, the area should be washed with soap and water. Following topical exposure, tingling, burning and redness have been observed. In the event of contact with the mucous membranes, these should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning throat and nausea have been reported.

If unopened vials are refrigerated, a precipitate may form that redissolves with little or no agitation upon reaching room temperature. Product quality is not affected. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.

The Chemo-Dispensing Pin device or similar devices with spikes should not be used since they can cause the vial stopper to collapse, resulting in loss of sterile integrity.

Preparation for IV administration: Prior to infusion, Paclitaxel 6mg/ml Concentrate for Solution for Infusion must be diluted, using aseptic techniques, in 0.9% sodium chloride injection, or 5% glucose injection, or 5% glucose and 0.9% sodium chloride

injection, or 5% glucose in Ringer's Injection, to a final concentration of 0.3 to 1.2 mg/mL.

Solutions prepared for infusion are stable for 24 hours at 25°C. Following multiple needle entries and product withdrawals, paclitaxel infusion multidose vials maintain microbial, chemical and physical stability for up to 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user. Diluted solutions should not be refrigerated.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. Paclitaxel infusion should be administered through an in-line filter with a microporous membrane $\leq 0.22\mu\text{m}$. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line filter.

There have been rare reports of precipitation during paclitaxel infusions, usually towards the end of a 24 hour infusion period. Although the cause of this precipitation has not been elucidated, it is probably linked to the supersaturation of the diluted solution. To reduce the precipitation risk, paclitaxel should be used as soon as possible after dilution and excessive agitation, vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use. During infusion the appearance of the solution should be inspected regularly and the infusion should be stopped if precipitation is present.

To minimise patient exposure to DEHP, which may be leached from plasticised PVC infusion bags, sets, or other medical instruments, diluted paclitaxel solutions should be stored in non-PVC bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Use of filter devices (eg. IVEX-2®) which incorporate short inlet and/or outlet plasticised PVC tubing has not resulted in significant leaching of DEHP.

Diluted solution should be for single use only.

Disposal: All items used for preparation, administration or otherwise coming into contact with paclitaxel injection should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

7. MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER

PL 04543/0487

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

05/07/2006

10 DATE OF REVISION OF THE TEXT

05/07/2006

Patient Information Leaflet

PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 04543/0487

PACKAGE LEAFLET

Paclitaxel 6mg/ml Concentrate for Solution for Infusion Paclitaxel

Read all of this leaflet carefully before you are given this medicine.
Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor or nurse.

In this leaflet:

1. What is paclitaxel and what is it used for?
2. Before you are given paclitaxel
3. How paclitaxel will be given to you
4. Possible side effects
5. Storing paclitaxel

The active substance in the injection is paclitaxel.

The other ingredients are citric acid (anhydrous), macrogol glycerol ricinolate, ethanol 96% and nitrogen.

Paclitaxel 6mg/ml Concentrate for Solution for Infusion is manufactured by EBEWE Pharma Ges.m.b.H. Nfg. KG, A-4866 Unterach, Austria for the Product Licence holder CP Pharmaceuticals Ltd, Ash Road North, Wrexham LL13 9UF.

1. WHAT IS PACLITAXEL CONCENTRATE FOR SOLUTION FOR INFUSION AND WHAT IS IT USED FOR?

Paclitaxel 6mg/ml Concentrate for Solution for Infusion is a concentrated form of paclitaxel which must be diluted before use. It is available in single vials containing 30mg of paclitaxel in 5ml, 100mg of paclitaxel in 16.7ml, 150mg of paclitaxel in 25ml and 300mg of paclitaxel in 50ml.

Paclitaxel 6mg/ml Concentrate for Solution for Infusion is a clear, colourless to pale yellow solution free from particles.

Paclitaxel belongs to a group of medicines known as cytotoxics, which are used in the treatment of cancer. Paclitaxel may be used to treat ovarian cancer, breast cancer, lung cancer and AIDS-related Kaposi's sarcoma.

2. BEFORE YOU ARE GIVEN PACLITAXEL CONCENTRATE FOR SOLUTION FOR INFUSION

You will not be given Paclitaxel Concentrate for Solution for Infusion:

- if you are allergic to paclitaxel or any of the other ingredients
- if you have a very low level of white blood cells in your blood
- if you have a serious infection
- if you are pregnant, breast-feeding or trying for a baby.

Your doctor will take special care when giving you paclitaxel:

- if you have liver problems
- if you are also receiving radiotherapy

Consult your doctor if any of the above warnings applies to you or has applied to you in the past.

Before your treatment starts you will be treated with a steroid (such as dexamethasone), an antihistamine (such as diphenhydramine) and an H₂-blocker (such as cimetidine). For certain types of treatment you may need to have your heart monitored before, during and after treatment with paclitaxel. Your doctor will also check your blood before, during and after every treatment. If the results of any of these tests are abnormal treatment will only be resumed when all readings are back to normal.

This medicinal product contains the ingredient macrogol glycerol ricinolate which may cause severe allergic reaction. If you know that you are allergic to this ingredient you should let your doctor know.

Pregnancy

Paclitaxel should not be given to you if you are pregnant, because it can cause serious birth defects.

Female patients should also avoid getting pregnant while being treated with paclitaxel and for at least six months afterwards. Male patients receiving paclitaxel should take adequate precautions to ensure that their partner does not become pregnant for the same period. If you are considering becoming parents after the treatment, you should discuss this with your doctor.

Men who wish to father children in the future should seek advice about freezing sperm before the paclitaxel treatment is started.

Breast-feeding

Paclitaxel should not be given to you if you are breast-feeding, as paclitaxel might pass into breast milk and affect the baby.

Driving and using machines:

Paclitaxel Concentrate for Solution for Infusion contains alcohol. Each treatment this will be the equivalent of taking two glasses of wine or four glasses of beer. This may cause side-effects which could affect your ability to drive. If this happens, you should avoid driving or operating machinery until these have worn off.

Being given paclitaxel at the same time as other medication

Paclitaxel is often used in combination with another drug, cisplatin. It is important that paclitaxel is administered before cisplatin. Care will be taken if you have gynaecological cancer and are being treated with paclitaxel and cisplatin.

If you have breast cancer you may be treated with another drug called doxorubicin. It is important that doxorubicin is given 24 hours after your treatment with paclitaxel.

Care is required if paclitaxel is administered at the same time as certain drugs which affect liver function including some drugs used to treat virus infections (e.g. ritonavir), some drugs used to treat depression (e.g. fluvoxamine) and rosiglitazone (used in diabetes). erythroycin and rifampicin, used to treat infections; fluoxetine, a drug used to treat depression; gemfibrozil, a drug used to treat heart disease; carbamazepine and phenytoin used for epilepsy, efavirenz and nevirapine, drugs used to treat HIV.

Care is required if paclitaxel is administered at the same time as protease inhibitors such as nelfinavir and ritonavir

Tell your doctor or pharmacist about medicines you are currently taking or have taken recently. This also applies to medicines you may have bought yourself from a pharmacy or supermarket.

3. HOW PACLITAXEL CONCENTRATE FOR SOLUTION FOR INFUSION WILL BE GIVEN TO YOU

Paclitaxel Concentrate for Solution for Infusion will only be given to you under the supervision of a doctor specialised in this type of treatment.

The dosage of paclitaxel depends on the condition you are being treated for, your response to the therapy and other medication you are being given. The paclitaxel concentrate should be diluted before use with a solution of sodium chloride or dextrose and given as an infusion (drip) into a vein.

When receiving paclitaxel for first-line treatment of ovarian cancer

The usual dosage of paclitaxel is 175mg per square metre of body surface area given over three hours, or 135mg per square metre of body surface area given over a 24 hour period, followed by treatment with 75mg of cisplatin per square metre of body surface area. There is a three week interval between each course of treatment.

When receiving paclitaxel for second-line treatment of ovarian cancer

The usual dosage of paclitaxel is 175mg per square metre of body surface area given over three hours, every three weeks for four courses of treatment.

When receiving paclitaxel for adjuvant treatment of breast cancer

The usual dosage of paclitaxel is 175mg per square metre of body surface area given over three hours. It is usually given in combination with another drug, trastuzumab. There is a three week interval between treatment courses.

When receiving paclitaxel for first-line treatment of breast cancer

The usual dosage of paclitaxel is 175mg per square metre of body surface area given over three hours. It is usually given in combination with another drug, trastuzumab. There is a three week interval between treatment courses.

Paclitaxel can also be used in combination with doxorubicin. The usual dosage is 220mg per square metre given over three hours with a three week interval between treatment courses.

When receiving paclitaxel for second-line treatment of breast cancer

The usual dosage of paclitaxel is 175mg per square metre of body surface area given over three hours. There is a three week interval between treatment courses.

When receiving paclitaxel for treatment of advanced non-small cell lung cancer

The usual dosage of paclitaxel is 175mg per square metre of body surface area given over three hours followed by treatment with 80mg of cisplatin per square metre of body surface area.. There is a three week interval between each course of treatment. Further treatments will depend on how well you react to the treatment.

When receiving paclitaxel for treatment of AIDS related Kaposi's Sarcoma

The usual dosage is 100mg per square metre given over three hours every two weeks.

Your general condition and your response to the treatment will be closely observed before, during and after the paclitaxel treatment.

4. POSSIBLE SIDE EFFECTS

Like any other medication, paclitaxel may cause side-effects, particularly if given in combination with other anticancer drugs and radiotherapy.

The most common unwanted effects are temporary hair loss, nausea, vomiting, diarrhoea, sore mouth, numbness and tingling in the hands and feet, aching muscles and joints, urinary tract and chest infections, flushing, rash, low blood pressure, blood problems and bradycardia (slowing of the heart beat).

Less commonly, paclitaxel may cause high or low blood pressure, heart problems, general weakness or paralysis, dizziness, fits (convulsions), problems with vision, loss of hearing and ringing in the ears, temporary hair loss, nail and skin discolouration, bowel problems, liver problems, or a serious rash with reddening and flaking of the skin, thrombosis (blood clot), temperature, chills, back pain, chest pain, stomach pain, pain in fingers and toes and sweating.

Rarely, paclitaxel may cause pneumonia, sepsis (an infection), leukaemia, loss of appetite, confusion, fits (convulsions) with dizziness and headache, problems with vision, loss of hearing and ringing in the ears, a heart rhythm problem known as atrial fibrillation, shock, breathing problems, cough, liver problems, bowel problems including constipation, pseudomembranous colitis (inflammation of the colon), a serious rash with reddening and flaking of the skin, general weakness or paralysis, high temperature, fluid retention, severe tiredness and dehydration.

As well as killing the cancer cells, the medicine may also affect some of your own cells especially the cells in your blood. This makes you more prone to infections and to bleeding or bruising easily. If you think you have an infection, a sore throat, mouth ulcers, fever, chills or achiness you should contact your doctor.

Swelling and pain (known as extravasation) may occur temporarily at the injection site. **If extravasation occurs, tell your doctor or nurse immediately.**

Allergic reactions to paclitaxel or to macrogol glycerol ricinolate can occur, with wheezing, flushing, a skin rash or swelling of your lips, eyes or tongue. You should contact your doctor **immediately** if you develop such symptoms.

Paclitaxel, in combination with radiation therapy, can cause inflammation of the lung with breathlessness. If you develop a persistent cough, experience pain or difficulty breathing or become breathless, you should seek medical attention.

Paclitaxel can harm unborn babies (see section on pregnancy). It may also affect fertility in men and women.

During the treatment with paclitaxel your general condition will be closely monitored.

If you notice any side-effects not mentioned in this leaflet, please tell your doctor or nurse.

5. STORING PACLITAXEL

Keep out of the reach and sight of children

Do not store above 25°C.

Store in the original container

Do not use after the expiry date stated on the label.

Chemical and physical in use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 25°C. Other in use storage times and conditions are the responsibility of the user.

This leaflet was prepared in February 2006

Labels/Packaging

PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 04543/0487



BATCH NUMBER AND EXPIRY DATE
TO BE OVERPRINTED

PACLITAXEL 6mg/ml
Concentrate for Solution for Infusion
5 ml vial
CARTON
Date:10/04/06
Colour: Green Pantone 3262, Black, Warm Red, Blue 312
Size 38mm x 38mm x 70mm

Mac File:
Mock-ups:
Paclitaxel 6mg/ml Concentrate 5ml vial CTN.ai

PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 04543/0487

Vial label



Batch number and expiry date to be overprinted

**Paclitaxel 6mg/ml
5ml vial label**
Mock-up 10/04/06
Size: 62mm x 21mm
Colours: Green 3262, Black, Blue 312

Mac File:
Mock-ups:
Paclitaxel 6mg/ml 5ml vial Label

PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 04543/0487



 OVERPRINT AREA

BATCH NUMBER AND EXPIRY DATE
TO BE OVERPRINTED

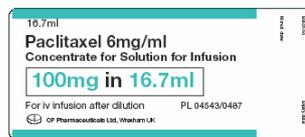
PACLITAXEL 6mg/ml
Concentrate for Solution for Infusion
16.7ml CARTON
Date: 10/04/06
Colour: Green Pantone 3262, Black, Warm Red
Size: 38mm x 38mm x 70mm

Mac File:
Mock-ups:
Paclitaxel 6mg/ml Concentrate 16.7ml vial CTN

PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 04543/0487

Vial label



Batch number and expiry date to be overprinted

Paclitaxel 6mg/ml
16.7ml vial label
Mock-up 10/04/06
Size: 71mm x 31mm
Colours: Green 3262, Black

Mac File:
Mock-ups:
Paclitaxel 6mg/ml 16.7ml vial Label

PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 04543/0487



 OVERPRINT AREA
BATCH NUMBER AND EXPIRY DATE
TO BE OVERPRINTED

Paclitaxel 6mg/ml
Concentrate for Solution for Injection or Infusion
25ml vial carton
Colour: Pantone Purple 2665, Green 3262, Black, Warm Red
Size: 48mm x 48mm x 83mm
Mock-up 10/04/06

Mac File:
Mock ups:
Paclitaxel 6mg/ml 25ml ctn

PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 04543/0487

Vial label



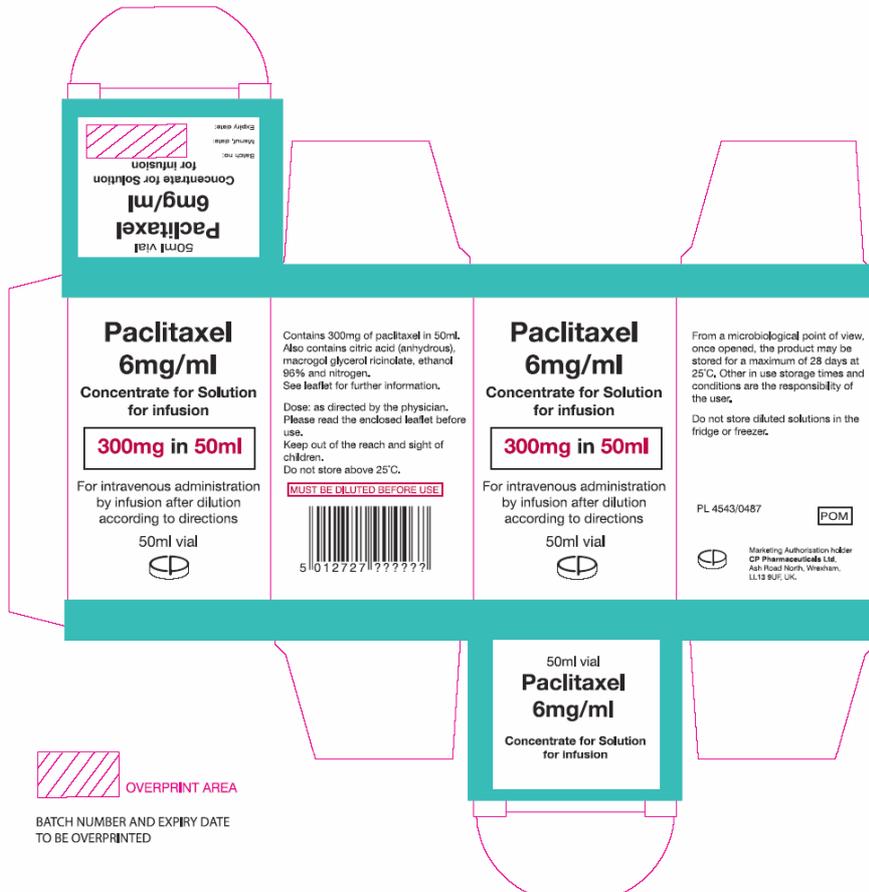
Batch number and expiry date to be overprinted

Paclitaxel 6mg/ml
25ml vial label
Mock-up 10/04/06
Size: 120mm x 40mm
Colours: Green 3262, Purple 2665, Black, Warm Red

Mac File:
Mock-ups:
Paclitaxel 6mg/ml 25ml vial Label

PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 04543/0487



 **OVERPRINT AREA**
BATCH NUMBER AND EXPIRY DATE
TO BE OVERPRINTED

Paclitaxel 6mg/ml
Concentrate for Solution for Injection or Infusion
50ml vial carton
Colour: Pantone Red 1945, Green 3262, Black, Warm Red
Size: 48mm x 48mm x 83mm
Mock-up 10/04/06

File:
Mock-up:
Paclitaxel 6mg/ml 50ml.ctn

PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 04543/0487

Vial label



Batch number and expiry date to be overprinted

Paclitaxel 6mg/ml
50ml vial label
Mock-up 10/04/06
Size: 120mm x 40mm
Colours: Green 3262, Red 1945, Black, Warm Red

Mac File:
Mock-ups:
Paclitaxel 6mg/ml 50ml vial Label